Complete Summary

GUIDELINE TITLE

Lipid management in adults.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Lipid management in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Jul. 72 p. [109 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Dyslipidemias, including:

- High low-density lipoprotein (LDL)-cholesterol
- High triglycerides
- Isolated low high-density lipoprotein (HDL)-cholesterol

GUIDELINE CATEGORY

Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Endocrinology
Family Practice
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Dietitians
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physicians

GUIDELINE OBJECTIVE(S)

- To improve the percentage of patients with known coronary heart disease (CHD) or equivalent with lipid disorders who meet their treatment goal
- To improve the percentage of patients without known coronary heart disease or equivalent with lipid disorders who meet their treatment goal
- To increase adherence with non-pharmacological treatment of patients with coronary heart disease or equivalent through education
- To improve the percentage of patients on lipid lowering medication who receive regular follow-up care for lipid disorder
- To increase the percent of patients on lipid lowering therapy who remain on therapy

TARGET POPULATION

Adults between the ages of 20 and 75 who are dyslipidemic

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Risk Assessment

1. Measurement of triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol; calculation of low-density lipoprotein (LDL)-cholesterol
2. Calculation of 10-year risk for coronary heart disease (CHD) or adding up cardiac risk factors
3. Evaluation for secondary causes of abnormal lipid levels, such as screening for diabetes and hypothyroidism, and consideration of other potential secondary causes in patients with elevated triglycerides
4. Establishment of lipid goals

Management/Treatment

1. Modification of lifestyle including:
    - Diet (American Heart Association Step 1 and II diet)

- Physical activity
- Weight management
- Aspirin
- Evaluation of alcohol consumption
- Multivitamins containing folic acid
- Smoking cessation
- Nutritional supplements containing B-sitosterol and/or sitostanol ester

2. Patient instruction in diet through a class or individually from a registered dietitian
3. Consideration of referral to a lipid clinic
4. Pharmacologic management
    - Statins [atorvstatin (Lipitor®), fluvastatin (Lescol®), lovastatin (Mevacor®), pravastatin (Pravachol®), simvastatin (Zocor®)]
    - Bile acid sequestrants [cholestyramine powder (Questran®, Questran® Lite, Prevalite®), colestipol powder and tablets (Colestid®), and colesevelam tablets (Welchol®)]
    - Niacin [crystalline (immediate release), SR (sustained release), ER (extended release) Niaspan®]
    - Niacin/statin combination products [niacin extended release plus lovastatin (Advicor®), Niaspan®/lovastatin]
    - Fibric acids [gemfibrozil (Lopid), fenofibrate (Tricor)]
    - Selective cholesterol absorption inhibitor [Ezetimibe (Zetia)]
5. Follow-up, including:
    - Assessment of adherence to therapy
    - Laboratory evaluations as indicated (such as fasting lipid panel, alanine aminotransferase (ALT) or aspartate aminotransferase (AST), creatinine phosphokinase (CPK), fasting blood sugar, and uric acid)
    - Consideration of secondary causes of hyperlipidemia
    - Adjustments in medication as needed
    - Consideration of referral to a lipid specialist
    - Reinforcement of adjunctive measures

MAJOR OUTCOMES CONSIDERED

- Risk of cardiovascular and cerebrovascular fatal and nonfatal events
- Lipoprotein measures, including triglyceride concentrations, high-density lipoprotein (HDL)-cholesterol, total cholesterol, and low-density lipoprotein (LDL)-cholesterol
- Safety, efficacy, cost, and side effects of drugs

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations:

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline draft, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member medical groups during an eight-week period of "Critical Review."

Each of the Institute's participating medical groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating medical groups following general implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group: Second Draft

Following the completion of the "Critical Review" period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary, and a written response is prepared to address each of the suggestions received from medical groups. Two members of the Cardiovascular Steering Committee carefully review the Critical Review input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of two questions: (1) Have the concerns of the medical groups been adequately addressed? (2) Are the medical groups willing and able to implement the guideline? The committee then either approves the guideline for pilot testing as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Medical groups introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occurs throughout the pilot test phase, which usually lasts for three months. Comments and suggestions are solicited in the same manner as used during the "Critical Review" phase.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Cardiovascular Steering Committee reviews the revised guideline and approves it for implementation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The recommendations for lipid management in adults are presented in the form of an algorithm with 16 components, accompanied by detailed annotations. An algorithm is provided for Lipid Management in Adults; clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) and conclusion grade (I-III, Not Assignable) definitions are repeated at the end of the "Major Recommendations" field.

Clinical Highlights

1. Treatment of hyperlipidemic patients without a history of coronary heart disease (CHD) or equivalent should be initiated when the patient and physician mutually agree upon a treatment plan after evaluation of the evidence about absolute risk reduction and the number needed to prevent a CHD event. (Annotations #3-6)
2. Instruct patients on adjunctive measures to help them maintain healthy lifestyles and reduce the risk of coronary events. These may include diet, physical activity, weight management, smoking cessation, and evaluation of alcohol consumption, multivitamin supplements with folic acid, aspirin therapy, and sitostanol ester nutritional supplement. (Annotations #3-6)
3. Treatment should be initiated for hyperlipidemic patients without a history of CHD or equivalent and 2 or more risk factors and whose low-density

lipoprotein (LDL)-cholesterol is greater than 130 mg/dL (goal less than 130 mg/dL) (Annotation #5)
4. Initiate a statin in patients who have a history of CHD or equivalent and LDL-cholesterol greater than 130 mg/dL. (Annotation #6)
5. Establish lipid goals based on the number of risk factors and LDL. (Annotations #3-6)
6. Patient adherence with recommended therapy should be evaluated during scheduled follow-up. (Annotation #13)

Lipid Management in Adults Algorithm Annotations

1. Patient has Dyslipidemia or is at High Risk for Coronary Heart Disease

   Secondary causes of abnormal lipid levels should be considered and treated when appropriate. Diet and exercise are the cornerstone of treatment for asymptomatic patients with dyslipidemia. Patients with an elevated LDL-cholesterol level should begin the American Heart Association (AHA) Step I diet and an individualized program of regular aerobic exercise. A diet low in fat, especially saturated fat, and high in soluble fiber is recommended. Patients who are overweight should be advised to reduce their calorie intake to achieve a modest weight loss. Patients should follow the diet and exercise program for a reasonable amount of time to determine whether their LDL-cholesterol level is lowered to the target range. For many asymptomatic patients, a diet and exercise program is sufficient.

   Evidence supporting this recommendation is of class: A

2. Calculate 10-Year Risk for CHD or Add Up Cardiac Risk Factors

   The National Cholesterol Education Program Adult Treatment Panel III defines high risk as a net of two or more (CHD) risk factors, which leads to more vigorous intervention. Identified risk factors are:

   - Age 45 years or older for men; age 55 years or older, or premature menopause without hormone replacement therapy, for women. CHD rates are higher in the elderly than in the young, and in men than in women of the same age.
   - A family history of premature CHD, defined as definite myocardial infarction (MI) or sudden death before age 55 in the father or a male primary relative, or before age 65 in the mother or a female primary relative
   - Currently smoking
   - Hypertension, defined as blood pressure greater than 140/90 mm Hg (confirmed by measurement on several occasions) or current use of any antihypertensive medication
   - Low high-density lipoprotein (HDL)-cholesterol level (less than 40 mg/dL)
   - Nontraditional risk factors (C-Reactive protein [CRP] and total homocysteine) have been shown to have some predictive values in screening vascular disease. The value of screening for these risk factors is not yet known.

Obesity and physical inactivity are not listed as risk factors, but should be considered as targets for intervention. Obesity operates through other risk factors (hypertension, hyperlipidemia, decreased HDL-cholesterol, and diabetes mellitus).

If HDL-cholesterol is 60 mg/dL or higher, one risk factor may be subtracted, because high HDL-cholesterol levels decrease CHD risk. (For example, if a patient has three risk factors but his or her HDL-cholesterol level is 60 mg/dL or higher, one risk factor is subtracted, leaving a total of two risk factors.)

Please refer to the table below, "Management" (Annotation Appendix A in the original guideline document).

Table: Management

<table>
<tr><th>Type of Dyslipidemia</th><th>Lipid Subfractions</th><th>Primary Therapy</th><th>Secondary Therapy</th></tr>
<tr><td rowspan="2">High LDL - cholesterol and triglycerides</td><td>LDL elevated
HDL ≥40
Triglycerides >200</td><td rowspan="2">• Weight loss
• Exercise
• Discontinue smoking
• No alcohol
• Improved diabetes mellitus control
• Step I/Step II low-concentrated carbohydrate diet</td><td>Statin
Niacin*</td></tr>
<tr><td>LDL elevated
HDL <40
Triglycerides >200</td><td>Statin
Niacin*
Fibric acids</td></tr>
<tr><td rowspan="2">High LDL-cholesterol</td><td>LDL elevated
HDL ≥40</td><td rowspan="2">• Weight loss
• Exercise
• Step I/Step II low-concentrated carbohydrate diet</td><td>Statin
Bile Acid Sequestrant
Niacin*
Fibric acids</td></tr>
<tr><td>LDL elevated
HDL <40</td><td>Statin
Bile Acid Sequestrant
Niacin*
Fibric acids</td></tr>
<tr><td>Isolated low HDL-cholesterol</td><td>HDL < 40
LDL is normal</td><td>• Exercise
• Discontinue smoking
• Discontinue excessive alcohol</td><td>(drug recommendations for treatment remain controversial except in CHD)</td></tr>
</table>

Type of Dyslipidemia	Lipid Subfractions	Primary Therapy	Secondary Therapy
			Niacin* Fibric acids**
High triglycerides		• Weight loss • Discontinue smoking • No alcohol • Improved diabetes mellitus control • Step I/Step II low-concentrated carbohydrate diet	Niacin* Fibric acids

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein

*Niacin can elevate glucose in patients with diabetes. Review the drug education sheet (provided in the original guideline document) with the patient when initiating Niacin therapy.

**Although not FDA-labeled, use of gemfibrozil is supported by the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study.

If considering combination therapy or alternative agents, suggest lipid clinic consultation.

Evidence supporting these recommendations is of classes: B, C, D, R

Please refer to Annotation Appendix B in the original guideline document, "Secondary Causes and Conditions Associated with Hyperlipidemia," for more information on secondary causes and conditions associated with hyperlipidemia.

3-6. Lifestyle Modification/Drug Therapy/Adjunctive Measures

Lifestyle modifications include diet, aerobic exercise, weight management, aspirin, evaluation of alcohol consumption, multivitamins containing folic acid, vitamins B6 and B12, smoking cessation, and nutritional supplement containing sitostanol ester. To avoid unintended toxic effects from vitamins, patients should be cautioned not to exceed recommended doses.

The decision to begin drug therapy must be based on a clinical discussion with the patient in which the evidence-based outcome data, possible side effects, and cost are weighed.

Please refer to the table above, "Management," (Annotation Appendix A in the original guideline document) and Annotation Appendix C, "Drug Companion Document" in the original guideline document for additional information.

Patients with risk factors for coronary heart disease but no history of disease who receive lipid lowering therapy are likely to experience a decreased risk of coronary artery disease with no effect on all-cause mortality. [Conclusion Grade I: See Discussion Appendix A, Conclusion Grading Worksheet - Annotation #3-6 (Risk Factors and Lipid Lowering Therapy) in the original guideline document.]

Patients with a history of coronary disease (including unstable angina and acute myocardial infarction) often benefit from treatment with a statin. Studies have consistently shown a decrease in risk of death from coronary heart disease. [Conclusion Grade I: See Discussion Appendix B, Conclusion Grading Worksheet - Annotations #3-6 (History of CHD)]

Occlusive Vascular Disease (OVD)

Occlusive vascular disease is defined as a diagnosis of carotid occlusive vascular disease, peripheral vascular disease, or both. Patients with occlusive vascular disease are at increased risk for CHD, even without clinical symptoms of CHD. Physicians should help such patients decide whether aggressive lipid lowering is indicated. (Patients who need aggressive lipid lowering can be managed according to the Patients with Known CHD algorithm on the second page of the original guideline document.) For patients with a history of stroke or cerebrovascular atherosclerosis, aggressive treatment with a statin-based regimen may be advisable.

Metabolic Syndrome

Specific recommendations for the management of lipid disorders in those with the metabolic syndrome have been described in recent national guidelines. The recommendations emphasize lifestyle management (weight loss, physical activity, dietary fat restriction). However, the risk of cardiovascular disease (CVD) is increased in these individuals, making lipid treatment complex. Specific treatment targets and recommendations have not been fully clarified. Further data will be required before more specific recommendations regarding the diagnosis and treatment of lipid disorders in this syndrome can be developed. These issues will be addressed in detail in future revisions of the guideline as more definitive data become available.

Hormone Replacement Therapy (HRT)

Recent studies, the Women's Health Initiative (WHI) and the Heart and Estrogen/Progestin Replacement Study (HERS II), did not find evidence that treatment with post-menopausal estrogen regimens provided any primary or secondary cardio-protective effect. Therefore, despite evidence suggesting a favorable effect on lipid profiles, estrogen or hormone replacement therapy cannot be recommended as a treatment for hyperlipidemia.

Other management strategies may include the following:

- American Heart Association Step II diet
- Aerobic exercise
- Weight management
- Folic acid
- Aspirin
- B-sitosterol and sitostanol ester (Take Control® and/or Benecol® margarines and salad dressings), if taken as directed

Evidence supporting these recommendations is of classes:

Diet: A, B, R
Aerobic Exercise: A, D, R
Weight Management: R
Hormone Replacement Therapy: A, B, R
Smoking Cessation: C, R
Evaluate Alcohol Consumption: B, R
Multivitamins Containing Folic Acid: B, C, D, M, R
Aspirin: Primary Prevention: A, B, M
Sitostanol Ester Nutritional Supplement: A, C

7. Management and Treatment

The patient should receive dietary instruction through a class or individually from a registered dietitian or trained professional. Adjunctive measures (see Annotation #15, "Adjunctive Measures") should be reinforced. Secondary causes should be considered. Lipid levels should be checked again in 6 to 8 weeks. Use of pharmacologic treatment is based on risk level and patient preference. Referral to a lipid clinic should be considered.

No primary prevention studies have addressed pharmacologic lipid treatment in persons at low risk for CHD, and there is no evidence to support drug treatment in this population. In particular, the incidence of CHD in men under 40 and premenopausal women is very low, and drug treatment in these groups is discouraged.

Primary prevention studies of pharmacologic lipid lowering have not shown a decrease in mortality, although most studies have shown about a 30 percent reduction in CHD events. Study populations have consisted of middle-aged

men, some with other risk factors. Similar benefit in higher-risk women can be assumed but has not been demonstrated.

The decision to begin and continue lipid-lowering medication should be made by the patient and the physician mutually.

Please refer to Table 3 in the original guideline document for a table on "Absolute Risk Reduction and Number Needed to Treat [NNT] with Pharmacologic Lipid Lowering.

The NNT can be presented to the patient as the number of people who would have to take medication for five years to prevent a non-fatal heart attack. (The major primary prevention studies have been 4-6 year studies). For example, if the NNT is 13, then 1 of 13 patients would benefit from treatment and 12 of 13 would not. Table 4 in the original guideline document lists primary prevention trials for prevention of CHD, including the type of therapy used and the NNT over 5 years for these trials.

Evidence supporting these recommendations is of classes: A, R

Treatment Options for Dyslipidemia

Reducing LDL-cholesterol (LDL-C) levels is the primary approach to lowering risk of CHD in both primary and secondary prevention. In some patients triglycerides may be elevated along with LDL-C so reducing triglycerides and increasing HDL-cholesterol (HDL-C) may also be desirable. Selection of drug therapy is dependent on several factors including lipoprotein levels and percent reduction needed to attain goal; concurrent drug therapies that could increase the risk of side effects occurring with specific lipid lowering drugs; presence of other medical disorders that may affect drug metabolism, increase risk of side effects, or be adversely affected by a specific lipid lowering drug.

Monotherapy

For the vast majority of patients, statins are the drugs of choice for lowering LDL-cholesterol. Aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing triglycerides and increasing HDL-cholesterol. The bile acid sequestrants, niacin, and fibric acids, and ezetimibe can also be used. Niacin has a greater effect on reducing triglycerides and increasing HDL-cholesterol than statins. The bile acid sequestrants are not systemically absorbed but may increase triglyceride levels. Fibric acids may be considered when triglycerides are elevated along with LDL-cholesterol, or for an isolated low HDL-cholesterol. Oral estrogen hormone replacement therapy (HRT) may increase triglyceride levels and should generally not be started in postmenopausal women. It may be continued on a case-by-case basis. Ezetimibe has modest LDL-cholesterol lowering effects as monotherapy.

Monotherapy of patients with hypertriglyceridemia depends on the triglyceride level. Patients with triglycerides greater than 500 mg/dL are at increased risk

of developing acute pancreatitis. This risk increases significantly as triglycerides increase to greater than 1,000 mg/dL. Fibric acids and niacin are the drugs of choice. Although triglycerides may not normalize with either drug, the risk of pancreatitis is reduced.

Combination Therapy

Some patients will require combination therapy. Most likely, these patients will have CHD. Using low doses of two complementary agents can often reduce LDL-cholesterol to a greater extent than a higher dose of either agent alone such as when a statin is combined with a bile acid sequestrant or ezetimibe with fewer side effects and possibly less cost. In very resistant cases, triple therapy may be needed.

In patients with mixed hyperlipidemia (increased LDL-cholesterol and triglycerides), the primary goal of decreasing LDL-cholesterol is the same as in patients with hypercholesterolemia alone. A high triglyceride (200 mg/dL-499 mg/dL) with hypercholesterolemia signals a relatively high risk of CHD. These patients often have a low HDL-cholesterol. Combination of a cholesterol lowering drug with triglyceride lowering drug, to achieve the non-HDL-cholesterol goal may be most warranted in patients with established coronary artery disease who are at very high risk of recurrent coronary events. Combining nicotinic acid with a statin is favorable for improving LDL-cholesterol, HDL-cholesterol, and triglycerides. Use of fibric acids leads to effective decrease in triglycerides and increased HDL-cholesterol, but effect on LDL-cholesterol is varied.

Please refer to Annotation Appendix C, "Drug Companion Document" in the original guideline document for information on drug efficacy, safety, risks, dosing, drug-food interactions, side effects, and monitoring.

9. LDL Goal Met?

If lipid goals are not met, it is important to intensify therapy until goals are reached. Lipid treatment is intensified within four months of an abnormal LDL value less than 20% of the time. This problem, referred to as "clinical inertia" is a major obstacle to improved lipid management.

10. HDL $\geq$40 and Triglycerides <200?

If the triglyceride level exceeds 400 mg/dL, the LDL-cholesterol level cannot be calculated according to the Friedewald formula. In such cases, a direct measurement of LDL-cholesterol, where available, can be used.

Non-HDL cholesterol becomes a secondary target when triglycerides are 200 to 499. The non-HDL target is 30 mg/dL higher than the LDL target. Non-HDL cholesterol is calculated by the formula non-HDL cholesterol = T cholesterol-HDL cholesterol.

11. Laboratory Monitoring in 3-12 Months

Refer to Annotation Appendix C, "Drug Companion Document" in the original guideline document.

Evidence supporting this recommendation is of class: R

12. Health Maintenance

Health maintenance includes periodic monitoring, risk factor modification, and reinforcement of adjunctive measures (see Annotation #15, "Adjunctive Measures").

13. Address Adherence

Asking non-threatening, open-ended questions during patient interviews can be a useful method of assessing medication adherence. The interview should include probes for factors that contribute to non-adherence including adverse reactions, misunderstandings of asymptomatic or chronic disease treatment, depression, cognitive impairment, complex dosing regimens, and financial constraints.

A. Assess the patient's knowledge of their medication and medical condition
B. Assess the patient's medication administration process
C. Assess the patient's barriers to adherence

To view sample assessment questions, refer to the original guideline document.

For more information on adherence, please refer to Annotation Appendix D, "NCEP Recommendations on Strategies to Improve Adherence" in the original guideline document.

14. Evaluation and Management

Evaluation of elevated triglycerides includes screening for diabetes and hypothyroidism and consideration of secondary causes. Use of fibric acid and niacin (nicotinic acid) should be considered, although considerable controversy exists regarding the benefits of medications. If triglycerides are greater than 500, triglyceride lowering drugs become first line therapy.

The clinician may wish to consider the use of fibric acid and niacin or statin therapy as well as screening the patient for diabetes mellitus (DM), hypothyroidism, or other secondary causes.

Uncontrolled glucose levels in patients with DM contributes to hypertriglyceridemia. Glucose levels in patients with diabetes should be under control to bring triglyceride levels under control.

Please refer to the table above, "Management" (Annotation Appendix A), Annotation Appendix B, "Secondary Causes and Conditions Associated with

Hyperlipidemia," and Annotation Appendix C, "Drug Companion Document" in the original guideline document.

Evidence supporting this recommendation is of class: A

15. Adjunctive Measures

Evidence suggests that adults with elevated lipid levels should follow the American Heart Association Step II diet or something more aggressive. Nutritional assessment and evaluation should be carried out by a registered dietitian whenever possible. Please refer to Annotations #3-6, "Lifestyle Modification/Drug Therapy/Adjunctive Measures" for additional information.

16. Follow-Up

A lipid profile should be obtained annually. If the patient is taking fibric acid or niacin, follow-up should be according to the recommended protocol.

Further management strategies include considering secondary causes of hyperlipidemia, increasing the dose of statin, considering the addition of niacin or a bile acid sequestrant, considering referral to a lipid specialist, and reinforcing adjunctive measures (see Annotation #15, "Adjunctive Measures").

Please refer to the table above, "Management," (Annotation Appendix A), Annotation Appendix B, "Secondary Causes and Conditions Associated with Hyperlipidemia," and Annotation Appendix C, "Drug Companion Document" in the original guideline document.

Evidence supporting this recommendation is of class: R

Definitions:

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
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B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

A detailed and annotated clinical algorithm is provided for Lipid Management in Adults.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting each recommendation. The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall Benefits

- Appropriate management of lipids in adults
- Improved percentage of patients with or without known coronary heart disease (CHD) or equivalent with lipid disorders who meet their treatment goal.
- Increased compliance with non-pharmacological treatment of patients with coronary heart disease or equivalent through education.
- Improved percentage of patients on lipid lowering medication who receive regular follow-up care for lipid disorder.

Specific Benefits

Efficacy of Drugs

- Statins. Substantial reductions in low-density lipoprotein (LDL)-cholesterol of 25 to 60 percent. Reductions in triglycerides are possible with all statins but are dependent on the baseline triglyceride level, the LDL-cholesterol lowering potency of the statin, and the dose utilized. The Scandinavian Simvastatin Survival Study (4S) trial reported reductions of 30 to 45 percent in deaths due to CHD, cardiovascular disease, and all causes after 4.5 years treatment with simvastatin in patients with CHD. The Heart Protection Study, utilizing 40 mg of simvastatin, reported a 24% reduction in first occurrence of major vascular events (non-fatal myocardial infarction [MI] or coronary death, non-fatal or fatal stroke, coronary or non-coronary revascularization) in a wide

range of high-risk individuals, 40 to 80 years of age, regardless of baseline cholesterol levels. The West of Scotland trial reported a 31 percent reduction in risk of non-fatal MI or death from CHD in men with hypercholesterolemia and no history of MI who were treated with pravastatin 40 mg daily. The Cardiovascular Adverse Risk Examination (CARE) study, using 40 mg of pravastatin daily, showed a 24 percent reduction in major coronary events in men and women with a mean LDL-cholesterol of 139 mg/dL who had survived a myocardial infarction. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) treatment with lovastatin 20 to 40 mg daily resulted in a 37 percent reduction in the risk of first major coronary events.

- Bile Acid Sequestrants. LDL-cholesterol was lowered 15 to 30 percent (dose dependent).
- Niacin. Exerts favorable effects on all lipids and lipoproteins and is good for mixed hyperlipidemia. Crystalline niacin reduces triglycerides 20 to 40 percent, increases high-density lipoprotein (HDL)-cholesterol 15 to 35 percent, and decreases LDL-cholesterol 6 to 25 percent. Extended release niacin (Niaspan) reduces triglycerides 11 to 35 percent, increases HDL-cholesterol 15 to 26 percent, and decreases LDL-cholesterol 9 to 17 percent. Sustained-release niacin reduces triglycerides 10 to 40 percent, increases HDL-cholesterol 5 to 15 percent and decreases LDL-cholesterol 6 to 50 percent (but this latter effect may be due to hepatic toxicity).
- Niacin/Statin Combination. Substantial effects on all lipid parameters (dose dependent) with decreases in LDL-cholesterol of 30 to 42 percent, increases in HDL-cholesterol 20 to 30 percent, and decreases in triglycerides 32 to 44 percent.
- Fibric acids. Triglycerides are reduced 30 to 50 percent; HDL-cholesterol increases 10 to 20 percent. Total cholesterol is only modestly reduced 5 to +20 percent in patients without elevated triglycerides. Effect on LDL-cholesterol is variable: fenofibrate may lower LDL-cholesterol more than gemfibrozil, but it is less effective than statins; HDL-cholesterol increases 10 to 20 percent (dependent on baseline triglyceride level).
- Ezetimibe. LDL-cholesterol is reduced about 18 percent. Ezetimibe may have an additive LDL-cholesterol lowering effect when used in combination with statins.

Subgroups Most Likely to Benefit

Fibric acids are good for severe hypertriglyceridemia in patients at risk for pancreatitis, for prevention of coronary heart disease (CHD) (not proven for fenofibrate) when patient has abnormal lipid triad of depressed high-density lipoprotein (HDL)-cholesterol, elevated low-density lipoprotein (LDL)-cholesterol, and elevated triglycerides. May be particularly useful in diabetics with mixed hyperlipidemia and for patients with dysbetalipoproteinemia. The Department of Veterans Affairs High-Density Lipoprotein Intervention Trial utilizing gemfibrozil, showed a 22 percent reduction in coronary heart disease death/nonfatal myocardial infarction in patients with documented coronary heart disease and low high-density lipoprotein-cholesterol as their primary lipid abnormalities.

POTENTIAL HARMS

Potential Side Effects of Drugs

- Statins. Mild gastrointestinal (GI) complaints, headache, and insomnia may occur. Myopathy is rare with monotherapy (0.1%) and appears to be dose dependent; risk is increased with combination therapy. Hepatotoxicity appears to be dose dependent with occurrence estimated at 0.1 to 2.3%.
- Bile acid sequestrants. Not absorbed, so limited to GI tract. Constipation is most common with cholestyramine and colestipol. Bloating and belching also occur.
- Nicotinic acid. Side effects include flushing, transient pruritis, acanthosis nigricans, GI upset, increased uric acid, increased serum glucose, and hepatotoxicity.
- Fibric Acids. GI most common; side effects also include dyspepsia, abdominal pain, diarrhea, and skin reaction. Rarely anemia, leukopenia, gallstones, atrial fibrillation, and myopathy may occur.
- Combination of nicotinic acid with a statin. An increased incidence of severe myopathy has been reported when a statin was combined with nicotinic acid or fibric acids.
- Ezetimibe. Abdominal pain, diarrhea, sinusitis, arthralgia, and back pain were all reported in >3% of patients, but similar to placebo.

Please refer to Annotation Appendix C, "Drug Companion Document," in the original guideline document for further information on safety concerns when using drug therapy.

CONTRAINDICATIONS

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Contraindications

- Statins: Absolute contraindications include active liver disease, pregnancy, lactation. Relative contraindications include alcohol abuse and primary biliary cirrhosis.
- Bile Acid Sequestrants: Absolute contraindications include complete biliary obstruction, bowel obstruction, triglycerides >400 mg/dL, and familial dysbetalipoproteinemia. Relative contraindications include triglycerides >200 mg/dL and patient on warfarin.
- Nicotinic acid: Absolute contraindications include active liver disease, active peptic ulcer, pregnancy/lactation, arterial hemorrhage, alcohol abuse, and severe gout. Relative contraindications include history of gout, high dose in type 2 diabetes mellitus (DM) or glucose intolerance, and renal dysfunction.
- Fibric acids: Absolute contraindications include severe hepatic impairment, and severe renal impairment. Relative contraindications include patients on warfarin.
- Combination of nicotinic acid with a statin. These combinations should generally be avoided in patients with acute or serious chronic illness (especially chronic renal disease), patients undergoing surgery or in patients who are already receiving cyclosporine, macrolide antibiotics, nefazodone, azole antifungal agents, or protease inhibitors.
- Ezetimibe: Absolute contraindications include use with statin in patients with active liver disease or unexplained persistent serum transaminase elevations. Relative contraindications include pregnancy, breast-feeding, moderate to severe hepatic insufficiency, and use with fibrates until studied in humans.

QUALIFYING STATEMENTS

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- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This medical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

RELATED NQMC MEASURES

- Lipid management in adults: percentage of patients with diagnosed coronary heart disease (CHD) or equivalent who have low-density lipoprotein (LDL)-cholesterol less than 100 mg/dL.
- Lipid management in adults: percentage of patients with diagnosed coronary heart disease (CHD) or equivalent who have a diet evaluation.
- Lipid management in adults: percentage of patients on a lipid lowering medication who have a fasting lipid panel every three to twelve months.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Lipid management in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Jul. 72 p. [109 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 Oct (revised 2003 Jul)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals

and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

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GUIDELINE COMMITTEE

Cardiovascular Steering Committee

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No work group members have potential conflicts of interest to disclose.

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GUIDELINE STATUS

This is the current release of the guideline.

It updates a previous version: Institute for Clinical Systems Improvement (ICSI). Lipid management in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2002 Jul. 61 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Treatment of lipid disorders in adults. In: ICSI pocket guidelines. April 2003 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2003 Mar. p. 102-3.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on July 10, 2000. The information was verified by the guideline developer on April 25, 2001. The summary was subsequently updated on August 17, 2001 following the withdrawal of the drug "Baycol (Cerivastatin)." The information was updated by ECRI on December 24, 2002. The information was verified by the guideline developer on January 23, 2003. The information was updated again by ECRI on April 16, 2004.

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